KINASE INHIBITOR

TECHNICAL FIELD

[0001] The present invention relates to a kinase inhibitor, a Hippo signal transduction pathway inhibitor, a therapeutic agent for a disease or tissue damage associated with failure of cellular proliferation, a proliferation promoter of a cell or tissue for a transplantation treatment, and a method for screening for a substance for treating and/or preventing a disease associated with promoted nuclear translocation of YAP and/or TAZ, and the like.

BACKGROUND ART

[0002] Kinases (protein phosphorylating enzymes, protein kinases) are enzymes that phosphorylate the hydroxyl groups of serine, threonine, or tyrosine in proteins, and are a group of enzymes responsible for signal transduction such as cell proliferation and differentiation. Not less than 500 kinds of genes encoding kinases have been cloned so far. Protein kinases are present throughout the cells and are deeply involved in the regulation and control of cell proliferation, differentiation, and functional expression (non-patent document 1).

[0003] Abnormal protein kinase activity has been confirmed in many diseases, and diseases are being treated by inhibiting protein kinase activity (non-patent document 2). For example, it is known that many oncogenes involved in canceration of cells encode protein kinases. Gleevec, a protein kinase inhibitor, is marketed as a therapeutic agent for chronic myeloid leukemia (non-patent document 3), and Herceptin is marketed as a therapeutic agent for breast cancer (patent document 1).

[0004] LATS1 and LATS2 (Large tumor suppressors 1 and 2) are protein kinases that are major factors constituting the Hippo signal transduction pathway (patent document 2, non-patent documents 4, 5). It is known that this transduction pathway is activated when the cell density increases and contact inhibition is applied, or when cells are injured by active oxygen, DNA damage, or the like (non-patent documents 6, 7, 8). When this transduction pathway is activated, LATS phosphorylates the transcriptional co-factor YAP (Yes-associated protein) or TAZ (transcriptional co-activator with PDZ-binding motif). Phosphorylated YAP or TAZ transfers from the cell nucleus to the cytoplasm and is subjected to proteolysis, thus suppressing the expression of the target gene of YAP or TAZ. Known examples of the genes whose expression is regulated by YAP include CCDN1, CTGF, BIRC2, CYR61, AMOTL2, TGFB2 and the like (non-patent documents 9, 10, 11, 12). Activation of the Hippo signal transduction pathway leads to the suppression of the expression of these genes, and causes suppression of cell proliferation and induction of cell death.

[0005] Hippo signal transduction pathway is known to regulate self-renewal and differentiation of stem cells (non-patent document 13). Hippo signal transduction pathway is necessary for maintaining the skin, intestines and nerves, and repair during tissue damage is inhibited unless YAP functions normally (non-patent document 14). Furthermore, deletion of the Hippo signal transduction pathway has been reported to ameliorate systolic heart failure after myocardial infarction (non-patent document 15). In this way, Hippo signal transduction pathway controls the proliferation, maintenance and recovery of cells, tissues and organs. Thus, inhibitors of the Hippo signal transduction pathway and activators of YAP and TAZ are expected to be therapeutic drugs for diseases caused by failure of cellular proliferation. Examples of such diseases include burn, trauma, muscular atrophy, ischemic diseases, and neurodegenerative diseases (e.g., Alzheimer's, Parkinson's and Huntington's diseases). As an example of an inhibitor of the Hippo signal transduction pathway, XMU-MP-1 has been reported as an inhibitor of MST1 (non-patent document 16). XMU-MP-1 has been shown to promote recovery from hepatopathy by inhibiting the Hippo signal transduction pathway. Furthermore, it has been reported that compounds that inhibit LATS1 and LATS2 have an effect of promoting repair of eyeball, skin and liver (patent document 3). In addition, IBS008738 has been reported as an activator of TAZ, and the effect of promoting recovery of muscle damage by this activator has been shown (non-patent document 17). As described above, a regulator of the Hippo signal transduction pathway is expected to be a therapeutic drug for various diseases.

DOCUMENT LIST

Patent Documents

[0006] patent document 1: U.S. Pat. No. 5,705,151
[0007] patent document 2: U.S. Pat. No. 5,994,503
[0008] patent document 3: WO 2018/198077

Non-Patent Document

[0009] non-patent document 1: Robert Roskoski Jr., Pharmacological Research 2016, 100: 1-23
[0010] non-patent document 2: Doriano F et al, Br J Pharmacol. 2015, 172(11): 2675-2700
[0011] non-patent document 3: Druker B J et al, Nat Med. 1996, 2(5):561-566
[0012] non-patent document 4: Justice R W et al, Genes Dev. 1995, 9(5):534-546
[0013] non-patent document 5: Hergovich A, Cell Biosci. 2013, 3(1):32
[0014] non-patent document 6: Pefani D E et al, FEBS J. 2016, 283(8):1392-1403
[0015] non-patent document 7: Meng Z et al, Genes Dev. 2016, 30(1):1-17
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[0018] non-patent document 10: Hong W et al, Semin Cell Dev Biol. 2012, 23(7):785-793
[0019] non-patent document 11: Gujral T S et al, Proc Natl Acad Sci USA. 2017, 114(18):E3729-E3738
[0020] non-patent document 12: Lee D H et al, Nat Commun. 2016, 7:11961
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